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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,367	12/27/2002	Rino Rappuoli	PP01651.102; 2302-1651	7808

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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	PAPER NUMBER
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/089,367	RAPPUOLI ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,21-25 and 27* is/are pending in the application.

4a) Of the above claim(s) *21-25 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 October 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 10/16/06 in response to the non-final Office Action mailed 04/25/06. With this, Applicants have amended the specification and the claims.

Status of Claims

2) Claims 1-9 have been amended via the amendment filed 10/13/06.

Claims 10-20, 26 and 28-34 have been canceled via the amendment filed 10/13/06.

Claims 1-9, 21-25 and 27 are pending.

Claims 1-9 are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

5) The objection to the specification made in paragraph 6 of the Office Action mailed 04/25/06 is withdrawn in light of Applicants' amendment to the specification.

Rejection(s) Moot

6) The rejection of claim 10 made in paragraph 7 of the Office Action mailed 04/25/06 under 35 U.S.C. § 112, first paragraph, as containing new matter, is moot in light of Applicants' cancellation of the claim.

7) The rejection of claim 15 made in paragraphs 9(c) and 9(d) of the Office Action mailed 04/25/06 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

8) The rejection of claims 12-20 made in paragraph 9(e) of the Office Action mailed

04/25/06 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

9) The rejection of claims 11-16 and 18-20 made in paragraph 11 of the Office Action mailed 04/25/06 under 35 U.S.C. § 103(a) as being unpatentable over Ryan *et al.* (*Immunology Lett.* 69: 59, # 11.19, June 1999 – Applicants' IDS) in view of Marsili *et al.* (EP 0 462 534 A2 – Applicants' IDS), is moot in light of Applicants' cancellation of the claims.

10) The rejection of claim 17 made in paragraph 12 of the Office Action mailed 04/25/06 under 35 U.S.C. § 103(a) as being unpatentable over Ryan *et al.* (*Immunology Lett.* 69: 59, # 11.19, June 1999 – Applicants' IDS) as modified by Marsili *et al.* (EP 0 462 534 A2 – Applicants' IDS) as applied to claims 16 and 11 above, and further in view of Metcalf (US 5,614,382) and Podda *et al.* (*Ann. Ig.* 3: 79-84, 1991), is moot in light of Applicants' cancellation of the claim.

Rejection(s) Withdrawn

11) The rejection of claims 1-9 made in paragraph 7 of the Office Action mailed 04/25/06 under 35 U.S.C. § 112, first paragraph, as containing new matter, is withdrawn in light of Applicants' amendment to the base claim.

12) The rejection of claims 1, 9, 11 and 19 made in paragraph 9(a) of the Office Action mailed 04/25/06 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn.

13) The rejection of claim 1 made in paragraph 9(b) of the Office Action mailed 04/25/06 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

New Rejection(s) Necessitated by Applicants' Amendment

The new rejection(s) set forth below are necessitated by Applicants' amendment to the claims.

Rejection(s) under 35 U.S.C. § 102

14) Claims 1-6, 8 and 9 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ryan *et al.* (*Immunology Lett.* 69: 59, # 11.19, June 1999, already of record) in view of Marsili *et al.* (EP 0 462 534 A2, already of record).

Ryan *et al.* taught a nasally delivered pertactin-containing acellular pertussis vaccine combined with a detoxified LTK63 or LTR72 (see abstract). Ryan's vaccine is therefore adapted for intranasal administration.

Ryan *et al.* do not expressly teach that their vaccine comprised a detoxified acellular pertussis holotoxin, detoxified diphtheria antigen or diphtheria toxoid, and a detoxified tetanus antigen or a tetanus toxoid.

However, Marsili *et al.* taught a vaccine comprising an acellular, non-toxic 9K/129G double mutant of pertussis holotoxin, filamentous haemagglutinin (FHA), and the 69 kilodalton protein or pertactin (i.e., additional non-diphtheria, non-tetanus and non-acellular pertussis antigen) in combination with diphtheria toxoid and tetanus toxoid (see abstract; claims, especially claim 6; Table on page 14; and Table X). Marsili *et al.* further taught that the non-toxic PT mutant, FHA, and the 69 Kd pertactin protein in their vaccine represent antigens of election for developing acellular anti-pertussis trivalent DPT vaccine having the desired features of high immunogenicity and absence of toxicity (see last full paragraph on page 4). Marsili *et al.* additionally taught the drawback of detoxifying a bacterial toxin by chemical detoxification using formaldehyde or glutaraldehyde by stating that such a method leads to reversion to toxicity (see page 2).

Given Marsili's express teaching that the non-toxic PT mutant, FHA, and the 69 Kd pertactin protein represent antigens of election for developing acellular anti-pertussis trivalent DPT vaccine having the desired features of high immunogenicity and absence of toxicity, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace Ryan's pertactin-containing acellular pertussis vaccine with Marsili's DTPa combination to produce the instant invention with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to produce the instant invention for the expected benefit of providing a trivalent acellular vaccine that advantageously has the desired features of high immunogenicity and absence of toxicity as taught by Marsili *et al.* in addition to having the ability to confer immunity against diphtheria and tetanus.

Claims 1-6, 8 and 9 are *prima facie* obvious over the prior art of record.

Rejection(s) under 35 U.S.C. § 103

15) Claim 7 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Ryan *et al.*

(*Immunology Lett.* 69: 59, # 11.19, June 1999, already of record) as modified by Marsili *et al.* (EP 0 462 534 A2, already of record) as applied to claims 6 and 1 above, and further in view of Metcalf (US 5,614,382, already of record) and Podda *et al.* (*Ann. Ig.* 3: 79-84, 1991, already of record).

The teachings of Ryan *et al.* as modified by Marsili *et al.* are explained above, which do not expressly disclose that the detoxified diphtheria antigen in their vaccine is CRM197.

However, the advantageous substitution of a diphtheria antigen with the non-toxic or detoxified, but immunologically indistinguishable CRM 197 in a vaccine was well known in the art at the time of the instant invention. For instance, Podda *et al.* expressly taught CRM197 to be an ideal candidate to substitute diphtheria toxoid in a vaccine (see summary). Metcalf taught that CRM197 is a non-toxic form of diphtheria toxin which is immunologically indistinguishable from the diphtheria toxin (see first full paragraph under 'Background').

Given Podda's express identification of CRM197 to be an ideal candidate to substitute diphtheria toxoid in a vaccine, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace diphtheria toxoid in Ryan's acellular pertussis vaccine as modified by Marsili's DTPa combination to produce the instant invention with a reasonable expectation of success. Given Metcalf's express teaching that the non-toxic CRM197 is immunologically indistinguishable from the diphtheria toxin, and Marsili's teaching that a chemically detoxified bacterial toxin has the disadvantage of reversion to toxic form, one of ordinary skill in the art would have been motivated to produce the instant invention for the expected benefit of providing a diphtheria antigen-containing combination DTPa vaccine that does not have the art-recognized drawback of reversion to toxicity.

Claim 7 is *prima facie* obvious over the prior art of record.

Remarks

16) Claims 1-9 stand rejected.

17) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE

MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

18) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted to the fax number (571) 273-8300 which receives papers 24 hours a day, seven days a week.

19) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Jeffrey Siew, can be reached on (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

January 2007

S. DEVI, PH.D.
PRIMARY EXAMINER